Quasielastic Neutron Scattering Study of Human α-Synuclein –Implication for Propensity for Amyloid Fibril Formation–

S. Fujiwara[1#], K. Araki[2], T. Matsuo[1], H Yagi[3], T Yamada[4], K. Shibata[5], and H. Mochizuki[2]

[1]*Quantum Beam Science Research Center, JAEA, Tokai, Ibaraki 319-1195, Japan*
[2] *Osaka University Graduate School of Medicine, Suita, Osaka, 565-0871, Japan*
[3]*Osaka University, Institute for Protein Research, Suita, Osaka, 565-0871, Japan*
[4] *Research Center for Neutron Science and Technology, CROSS-Tokai, Tokai, Ibaraki, 319-1106, Japan*
[5] *J-PARC Center, Tokai, Ibaraki 319-1195, Japan*

 # Corresponding author: fujiwara.satoru@jaea.go.jp

α-synuclein (α-Syn) is an intrinsically disordered protein consisting of 140 amino acid residues. Although its function is unknown, the filamentous aggregates (amyloid fibrils) of α-Syn have been shown to be involved with pathogenesis of a neuro-degenerative disorder, Parkinson's disease. Elucidation of the mechanism of amyloid fibrils formation of α-Syn is important for understanding the mechanism of pathogenesis of this disease. Propensity for amyloid fibril formation of α-Syn is sensitive to environmental conditions. In particular, α-Syn at low pH is more prone to form fibrils than at neutral pH [1]. Comparison of the behavior of α-Syn at low and neutral pH should thus provide insights into the mechanism of amyloid fibril formation of α-Syn.

Here we employ quasielastic neutron scattering (QENS) to investigate the "dynamic" behavior of α-Syn at low and neutral pH. We prepared the solution samples of α-Syn at pH 3.0 and 7.4 in D_2O. The fibrils were yet to be formed in these conditions. We also prepared the solution samples of α-Syn in fibril state for comparison. The QENS experiments on these samples were carried out using a high energy resolution near-backscattering spectrometer, BL02 (DNA), at MLF/J-PARC. Analysis of the QENS spectra showed that α-Syn at low pH is more flexible than in neutral pH, suggesting that the different propensity for amyloid fibril formation arises from differences in kinetics. It was also shown that amplitudes of the local motions increase in fibril state. Since the amplitudes of the local motions could be an indication of a distribution of conformational substates, this result suggests that the fibril state is entropically favorable.

Reference

[1] V. N. Uversky, J. Li, A. L. Fink, J. Biol. Chem., **276**, 10737-10744 (2001).